



Real-world treatment patterns and impact of comorbidity burden on treatment duration for patients with ALK+ NSCLC in the US

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Background

- An analysis of real-world data on the treatment of non-small cell lung cancer (NSCLC) in patients with anaplastic lymphoma kinase gene rearrangements (ALK+) conducted from January 2011 to June 2018 identified an unmet need for effective treatments.¹
 - Median real-world progression-free survival (wPFS) for first- and second-line ALK tyrosine kinase inhibitor (TKI) therapy was <8 months; crizotinib was most commonly used for first-line treatment (84.6% of patients); median time to treatment discontinuation (TTD) of first-line ALK TKI therapy was 7 months.
- The treatment landscape for patients with ALK+ NSCLC is evolving, with several new next-generation ALK TKIs receiving FDA approval for first-line treatment:
 - Ceritinib (approved on May 28, 2017),² alectinib (November 6, 2017),³ brigatinib (May 22, 2020),⁴ and lorlatinib (March 3, 2021).⁵
- Next-generation ALK TKIs are considered standard of care.⁶
- Comorbidities are frequent in patients with lung cancer and have an impact on diagnostic and therapeutic management.⁷
- No studies have described recent treatment patterns among patients with ALK+ NSCLC or assessed the impact of comorbidity burden on the treatment duration of next-generation ALK TKIs.

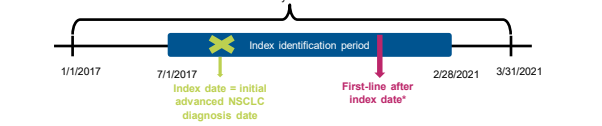
Objectives

- This study aimed to describe treatment patterns of patients with advanced/metastatic ALK+ NSCLC in recent years (2018 to 2021) and to evaluate the impact of comorbidity burden on duration of first-line treatment with next-generation ALK TKIs.

Methods

- Study Design**
 - This was a retrospective, observational study using a large US Commercial and Medicare Supplemental database.
 - Index date was defined as the date of advanced/metastatic NSCLC diagnosis.
 - Pre-index period was defined as 6 months prior to index date.
 - Post-index was defined as the time from the index date to the end of study period or loss to follow-up.

Figure 1. Study Design



*Only first-line treatments initiated on or after January 1, 2018, were included to capture the most recent treatment patterns. NSCLC, non-small cell lung cancer.

Data Source
A large US claims database (IBM® MarketScan® Research database), including commercially insured and Medicare supplemental data, was used for this study.

Patient Population
Adult patients diagnosed with advanced/metastatic lung cancer (i.e., index date) who had continuous enrollment in the health plan for ≥6 months before and ≥1 month after index date were identified.
Patients must have been treated with at least one ALK TKI and initiated first-line treatment from January 1, 2018, to February 28, 2021 (Table 1).

Table 1: Patient Selection

Inclusion/Exclusion Criteria	N
Included patients with ≥1 inpatient claim or ≥2 outpatient claims ≥30 days apart within 1 year of a lung cancer diagnosis ^a	223,583
Included patients with advanced/metastatic diagnosis on or after initial lung cancer diagnosis between January 1, 2017, and February 28, 2021 ^{b,c}	26,498
Included patients who received at least one ALK inhibitor (alectinib, ceritinib, crizotinib, lorlatinib, brigatinib) after initial advanced/metastatic lung cancer diagnosis	518
Remaining patients after excluding those who did not have at least 6 months continuous enrollment in the pre-index period	312
Remaining patients after excluding those who did not have at least 1 month of continuous enrollment in the post-index period	310
Remaining patients after excluding those who did not receive first-line treatment on or after January 1, 2018	219
Remaining patients after excluding those who were <18 years old at the index date	210

^aICD-9 codes: I62.x, I62.0x, I62.2x, I62.4x, I62.5x, I62.8x, I62.9x; ICD-10 C34.x, C34.0x, C34.1x, C34.2, C34.3, C34.8x, C34.9x
^bICD-10 codes: C34.8, C77.1, C77.0, C77.2, C77.3, C77.4, C77.5, C77.8, C77.9, C78.x, C79.x
^cThe index date was the initial advanced/metastatic diagnosis date.
ALK, anaplastic lymphoma kinase; ICD-9/10, International Classification of Diseases, 9th/10th revision.

Comorbidity Burden
The comorbidity burden was evaluated using the Charlson Comorbidity Index (CCI) during the pre-index period.^{10,11} The CCI is a validated index that takes into account the number and seriousness of comorbid diseases.^{10,11}
It includes 19 chronic conditions, including chronic obstructive pulmonary disease (COPD), that were selected and weighted according to the degree of their association with mortality.^{10,11}

Outcome Measures
TTD: defined as the time from initiation of first-line treatment until the end of that treatment. TTD was censored if patients were still on first-line treatment at the end of the follow-up.

Statistical Analysis
Patient characteristics and treatment patterns were summarized using standard descriptive statistics.
The TTD was analyzed using the Kaplan-Meier method, stratified by CCI (CCI = 0, CCI = 1, or CCI ≥2). Cox proportional hazard model was used to estimate the associations between comorbidity burden, as a categorical variable, and the TTD. The model was adjusted for age, gender, the brain metastasis status before first-line, and the smoking status.

Results

Baseline Characteristics
A total of 219 patients with advanced/metastatic ALK+ NSCLC received first-line treatments.
Median age was 56 years (range, 25 – 97 years), and 54% of patients were female (Table 2).
Median follow-up was 12.1 months (range, 0.4 – 39.0 months).
83.4% of patients had CCI ≥1, and 31.5% of patients had a diagnosis of brain metastasis prior to first-line treatment (Table 2).
The most common comorbidities were COPD (26.9%), mild liver disease (16.9%), and uncomplicated diabetes mellitus (16.4%).

Table 2: Baseline Demographics and Clinical Characteristics (N=219)

Gender	n (%)	Region	n (%)
Female	118 (53.9)	West	36 (16.4)
Male	101 (46.1)	Other/Unknown	37 (16.9)
Age category, years	Insurance type	n (%)	
18 - 39	PPO	107 (48.9)	
40 - 64	HMO/EPO	32 (14.6)	
65 - 74	POS	19 (8.7)	
75+	CDHP	22 (10.0)	
	HDHP	25 (11.4)	
	Other	14 (6.4)	
CCI	Smoking status	n (%)	
0	Current smoker	9 (4.1)	
1	Previous smoker	29 (13.2)	
≥2	Non-smoker/Unknown	181 (82.6)	
Region	Brain metastasis diagnosis prior to first-line treatment	n (%)	
Midwest	With brain metastasis	69 (31.5)	
Northeast	Without brain metastasis	150 (68.5)	
South			

CCI, Charlson Comorbidity Index; CDHP, consumer-driven health plan; EPO, exclusive provider organization; HDHP, high deductible health plan; HMO, health maintenance organization; POS, point of service; PPO, preferred provider organization.

Treatment Patterns
First-line Treatment
Most patients received next-generation ALK TKIs as first-line treatment at the time of data cut (Table 3).
53% of patients were treated with first-line alectinib, 1% of patients were treated with first-line brigatinib, and 1% of patients were treated with first-line ceritinib.
Approximately 20% of patients were treated with first-line crizotinib, and 9% of patients were treated with first-line chemotherapy alone (Table 3).

Table 3: First-line Treatment (N=219)

Treatment	n (%)
Next-generation ALK TKIs	120 (55.0)
Alectinib	116 (53.2)
Brigatinib	2 (0.9)
Ceritinib	2 (0.9)
Crizotinib	43 (19.5)
ALK TKI + chemotherapy	16 (7.3)
18 - 39	11 (9.2)
40 - 64	93 (77.5)
65 - 74	3 (2.5)
75+	13 (10.8)
Chemotherapy alone	20 (9.1)
Chemotherapy + immuno-oncology	13 (5.9)
Immuno-oncology alone	4 (1.8)
Other	3 (1.4)

ALK, anaplastic lymphoma kinase; TKI, tyrosine kinase inhibitor.

Second-line Treatment
35% of patients received second-line treatments.
The majority of the second-line treatments were next-generation ALK TKIs (57%), including alectinib, brigatinib, and lorlatinib (Table 4).
14% of patients were treated with crizotinib as second-line treatment, and 14% of patients were treated with chemotherapy alone or chemotherapy plus immuno-oncology as second-line treatment (Table 4).

Table 4: Second-line Treatment (N=76)

Treatment	n (%)
Next-generation ALK TKIs	43 (56.6)
Alectinib	22 (28.9)
Brigatinib	7 (9.2)
Lorlatinib	14 (18.4)
Crizotinib	11 (14.5)
ALK TKI + chemotherapy	5 (6.6)
Chemotherapy alone	8 (10.5)
Chemo + immuno-oncology	3 (3.9)
Immuno-oncology alone	2 (2.6)
Other	4 (5.3)

ALK, anaplastic lymphoma kinase; TKI, tyrosine kinase inhibitor.

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Results

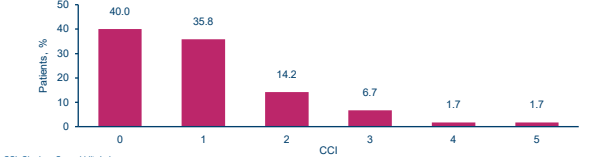
Comorbidity Burden in Patients Treated With First-line Next-generation ALK Inhibitors
A total of 120 patients were treated with first-line next-generation ALK inhibitors.
Common comorbidities in patients receiving first-line next-generation ALK inhibitors included chronic pulmonary disease, mild liver disease, diabetes (without chronic complication), and congestive heart failure (Figure 2).

Figure 2. Distribution of Comorbidity Conditions (N=120)



Most patients (75.8%) treated with first-line next-generation ALK inhibitors had CCI of 0 or 1 (Figure 3).

Figure 3. Distribution of CCI score (N=120)



CCI, Charlson Comorbidity Index.
In these patients, demographic and clinical characteristics were described across CCI categories (Table 5).

Table 5. Baseline Demographics and Clinical Characteristics in Patients Treated With First-line Next-generation ALK TKIs, Stratified by CCI (N=120)

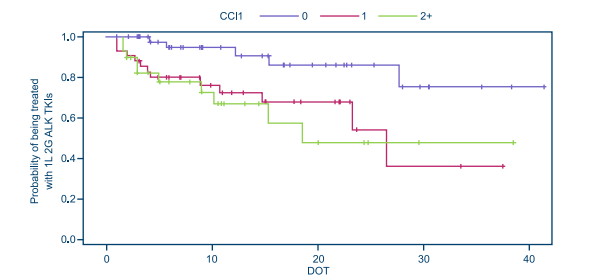
	Total (N=120)	CCI = 0 (n = 48)	CCI = 1 (n = 43)	CCI ≥2 (n = 29)	P value
Gender					0.7616
Female	68 (56.7)	27 (56.3)	26 (60.5)	15 (51.7)	
Male	52 (43.3)	21 (43.8)	17 (39.5)	14 (48.3)	
Age category, years					0.1010
18 - 39	11 (9.2)	4 (8.3)	5 (11.6)	2 (6.9)	
40 - 64	93 (77.5)	41 (85.4)	32 (74.4)	20 (69.0)	
65 - 74	3 (2.5)	2 (4.2)	1 (2.3)	0 (0)	
75+	13 (10.8)	1 (2.1)	5 (11.6)	7 (24.1)	
Region					0.4206
Midwest	29 (24.2)	13 (27.1)	9 (20.9)	7 (24.1)	
Northeast	19 (15.8)	9 (18.8)	7 (16.3)	3 (10.3)	
South	37 (30.8)	16 (33.3)	12 (27.9)	9 (31.0)	
West	17 (14.2)	8 (16.7)	5 (11.6)	4 (13.8)	
Other/Unknown	18 (15.0)	2 (4.2)	10 (23.3)	6 (20.7)	
Insurance type					0.1312
PPO	57 (47.5)	18 (37.5)	21 (48.8)	18 (62.1)	
HMO/EPO	19 (15.8)	4 (8.3)	11 (25.6)	4 (13.8)	
POS	11 (9.2)	8 (16.7)	1 (2.3)	2 (6.9)	
CDHP	10 (8.3)	5 (10.4)	4 (9.3)	1 (3.4)	
HDHP	15 (12.5)	8 (16.7)	5 (11.6)	2 (6.9)	
Comprehensive	7 (5.8)	4 (8.3)	1 (2.3)	2 (6.9)	
Missing	11 (9.2)	1 (2.1)	0 (0)	0 (0)	
Smoking status					0.4674
Current smoker	3 (2.5)	1 (2.1)	0 (0)	2 (6.9)	
Previous smoker	11 (9.2)	4 (8.3)	4 (9.3)	3 (10.3)	
Non-smoker/Unknown	106 (88.8)	43 (89.6)	39 (90.7)	24 (82.8)	
Brain metastasis diagnosis prior to first-line treatment	49 (40.8)	17 (35.4)	17 (39.5)	15 (51.7)	0.3612

ALK, anaplastic lymphoma kinase; CCI, Charlson Comorbidity Index; CDHP, consumer-driven health plan; EPO, exclusive provider organization; HDHP, high deductible health plan; HMO, health maintenance organization; POS, point of service; PPO, preferred provider organization; TKI, tyrosine kinase inhibitor.

Results

TTD of First-line Next-generation ALK TKIs
Among patients treated with first-line next-generation ALK TKIs (n=120), overall median TTD was not reached.
Median TTD stratified by CCI was: not reached for CCI = 0 (n = 48); 26.5 months (95% CI: 14.8-NA) for CCI = 1 (n = 43); and 18.5 months (95% CI: 10.2-NA) for CCI ≥2 (n = 29) (Figure 4).

Figure 4. TTD for Patients Treated with First-line Next-generation ALK TKIs (N = 120), Stratified by CCI (0, 1, or ≥2)



1L, first-line; 2G, second-generation; ALK, anaplastic lymphoma kinase; CCI, Charlson Comorbidity Index; TTD, time to treatment discontinuation; TKI, tyrosine kinase inhibitor.

After adjusting for age, gender, baseline brain metastasis status, and smoking status, patients with CCI ≥2 and CCI = 1 had increased risk of discontinuing first-line treatment compared to patients with CCI = 0 (Table 6).

Table 6. Adjusted Analysis of TTD Among Patients Treated with First-line Next-generation ALK TKIs (N=120)

Variable	Reference	HR	95% CI	P value
CCI = 1	CCI = 0	4.05	1.41 - 11.64	0.009
CCI ≥2	CCI = 0	5.42	1.74 - 16.86	0.004
Age 40-64 years		0.68	0.16 - 3.00	0.611
Age 65+ years	Age 18-39	0.56	0.10 - 3.18	0.509
Male	Female	0.83	0.38 - 1.80	0.639
Brain metastasis prior to first-line - Yes	No	0.67	0.29 - 1.56	0.353
Current smoker	Non-smoker/Unknown	1.53	0.19 - 12.50	0.690
Previous smoker	Unknown	<0.01	0.0 - NA	0.989

ALK, anaplastic lymphoma kinase; CCI, Charlson Comorbidity Index; CI, confidence interval; HR, hazard ratio; TKI, tyrosine kinase inhibitor.

Limitations

- Limitations of this study include those inherent to observational studies, such as the potential for selection bias or confounding.
- This study was limited to individuals included in this claims database in the United States and may not be representative of a broader population.
- Clinical reasons for treatment discontinuation are not known.
- Some demographic characteristics, including ethnicity, occupation, and economic status, that may be associated with comorbidities were not available in the claims database.

Discussion

- In this retrospective analysis of claims data from 2018, the most common first-line treatments among patients with advanced/metastatic ALK+ NSCLC were next-generation ALK TKIs, followed by crizotinib and chemotherapy.
- Comorbidities, including COPD, mild liver disease, and uncomplicated diabetes mellitus, were common in this patient population.
- Higher comorbidity burden, as measured by a composite CCI, was associated with increased risk of treatment discontinuation among patients receiving current first-line next-generation ALK TKIs (primarily alectinib), suggesting unmet medical need of current therapy.
- Evaluation of the effectiveness of additional novel therapies for first-line treatment will be made in future studies. Prompt management for controlling comorbidity in the care of patients with ALK+ advanced/metastatic NSCLC may be important.

Disclosures

Yin Wan, Kaili Ren, Huamao M Lin, Yanyu Wu, and Pingkuan Zhang are employees of Takeda Development Center Americas, Inc. and may own stock. Michael J Humphries is an employee of Takeda Pharmaceuticals U.S.A., Inc. and may own stock. Mohammad Jahanzeb has received research grants from Eli Lilly, Boehringer Ingelheim, Callisto, and Takeda; has been an invited speaker for Novartis and Roche/Genealogy; and has received consulting fees from Pfizer, Takeda, Puma, BMS, AstraZeneca, and Merck.

Presented at the World Conference on Lung Cancer 2022
August 6-9, 2022

Acknowledgements

Medical writing assistance was provided by Jane Kondziejewski, PhD of SNELL Medical Communications, Inc. and funded by Takeda Development Center Americas, Inc.

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